Does Low-Dose Acetylsalicylic Acid Prevent Stroke After Carotid Surgery?  
A Double-blind, Placebo-Controlled Randomized Trial

Bengt Lindblad, MD, PhD; Nils H. Persson, MD, PhD; Rabbe Takolander, MD, PhD; David Bergqvist, MD, PhD

**Background and Purpose:** The aim of this randomized double-blind, placebo-controlled trial was to evaluate whether neurological deficits could be prevented with low-dose acetylsalicylic acid (ASA) as an adjunct to carotid endarterectomy.

**Methods:** A total of 232 patients were randomized to two groups, 75 mg/d ASA starting preoperatively and continued for 6 months (n=117) or placebo (identical tablets) (n=115). The patients were followed up regularly for 1 year.

**Results:** The groups were well matched regarding laboratory data and indication for operation. The number of patients with intraoperative or postoperative stroke without complete recovery within 1 week were 0 and 2 at 30 days and 6 months, respectively, in the ASA group, compared with 7 and 11 in the placebo group (P=.01). Including all neurological events within 6 months, this was found in 15 patients in the ASA group compared with 24 in the placebo group (P=.12). Mortality was 0.8% and 3.4% at 30 days and 6 months, respectively, in the ASA group. In the placebo group, the corresponding figures were 4.3% and 6.0%, respectively (P=.12). The intraoperative bleeding did not differ between the groups nor did the number of reoperations due to bleeding or other complications related to pharmacology.

**Conclusions:** This study indicates that low-dose ASA (75 mg/d) reduces the number of postoperative strokes without complete recovery within 1 week. Overall neurological events are insignificantly reduced, as also mortality. The use of low-dose ASA (75 mg) seems safe and effective in reducing cerebrovascular events after carotid endarterectomy. *(Stroke 1993;24:1125-1128)*

**KEY WORDS** • aspirin • carotid endarterectomy • clinical trials

The use of acetylsalicylic acid (ASA) after transient ischemic attacks has been shown to reduce the risk of recurrent cerebrovascular incidents.1-4 In a meta-analysis including more than 8600 patients, a risk reduction was found with ASA of 22% for major vascular events (myocardial infarction, stroke, and vascular death), and for nonfatal stroke.5 Additionally, in other studies ASA has been shown to reduce reinfarction and sudden death in patients after heart infarction and unstable angina.6-8

The aim of carotid endarterectomy is to prevent stroke. The European and North American multicenter trials9,10 have shown carotid surgery to be beneficial in symptomatic patients with severe stenosis on optimal pharmacological therapy, usually ASA. The effect on intermediate degree stenosis is still under evaluation.

Although pharmacological therapy has been commonly used after carotid surgery, little is known about the effect of such a therapy. Fields and coworkers4 reported a reduction of postoperative neurological events (including retinal infarction, transient ischemic attack, stroke, and fatal stroke) with ASA. However, they did not start therapy until the fifth postoperative day. In a study by Boysen and coworkers,11 low-dose ASA starting one to several weeks postoperatively did not show any risk reduction compared with placebo treatment. We previously12 reported an incidence of neurological deficit of 12% during the first 6-month period after surgery; thereafter, the incidence was about 1% per year. The intention of this study was to elucidate the value of ASA started preoperatively as prophylaxis against neurological complications in the postoperative period after carotid surgery.

**Materials and Methods**

A total of 232 patients undergoing carotid endarterectomy were randomized to either placebo or 75 mg ASA (Trombyl; Leo, Helsingborg, Sweden) once daily for 6 months. Primary end points were intraoperative or postoperative cerebrovascular events and mortality.

All consecutive patients (280) who underwent carotid surgery from December 1985 to February 1991 were eligible to participate. Exclusion criteria were active peptic ulcer, hypersensitivity to ASA, or treatment with oral anticoagulants for reasons other than cerebrovascular protection.

A total of 48 patients did not fulfill the inclusion criteria or did not want to participate. The remaining 232 patients were supplied with individually prepared...
TABLE 1. Patient Characteristics and Reasons for Surgery

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Placebo group (n=115)</th>
<th>ASA group (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median and range; years)</td>
<td>66 (40-81)</td>
<td>66 (48-79)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ischemic heart disease (%)</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Diabetics (%)</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Smokers (%)</td>
<td>44</td>
<td>49</td>
</tr>
<tr>
<td>No risk factors (%)</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>Cholesterol (median and range; mmol/L)</td>
<td>6.7 (4.3-10.7)</td>
<td>6.7 (3.7-10.6)</td>
</tr>
<tr>
<td>Triglycerides (median and range; mmol/L)</td>
<td>1.9 (0.6-7.4)</td>
<td>1.7 (0.4-6.1)</td>
</tr>
<tr>
<td>Hematocrit (median and range; %)</td>
<td>43 (30-57)</td>
<td>42 (31-52)</td>
</tr>
<tr>
<td>Creatinine (median and range; umol/L)</td>
<td>96 (54-554)</td>
<td>95 (62-195)</td>
</tr>
<tr>
<td>Platelet count (median and range; 10^9/L)</td>
<td>228 (114-435)</td>
<td>221 (124-477)</td>
</tr>
</tbody>
</table>

Reason for carotid surgery

| Amaurosis fugax (%) | 19 | 19 |
| Hemispheric TIA (%) | 33 | 36 |
| Asymptomatic stenosis in symptomatic patient (%) | 7 | 10 |
| Minor stroke (%) | 41 | 35 |

TIA indicates transient ischemic attack.

and numbered boxes with identical tablets for ASA or placebo. The treatment was started on the evening before surgery, and usually the patients could continue the therapy on the evening after the operation and thereafter once daily during the first 6 months. If the patient reached an end point, the study drug was discontinued and further treatment depended on the patient’s situation. Usually ASA was used.

The end points of the study were all types of cerebrovascular events and mortality within 6 months. Cerebrovascular events were classified as stroke without complete recovery within 1 week, stroke with complete recovery within 1 week, transient ischemic attack and/or amaurosis fugax, event from the contralateral hemisphere subdivided into stroke, and transient ischemic attack.

Before surgery the patients were characterized regarding risk factors and smoking habits (hypertension, antihypertensive therapy; ischemic heart disease, previous myocardial infarction, angina pectoris, or ECG compatible with myocardial ischemia; peripheral vascular disease, claudication; diabetes, insulin- and pharmacologically treated diabetes; smoking, consumption of over five cigarettes/day). Cholesterol and triglycerides were measured, as were hematocrit, serum creatinine, and platelet count. Preoperative electrocardiograms were analyzed for ischemic changes. Preoperatively, an angiogram was performed (1 day to 3 months before surgery), and on the day before surgery a duplex examination of the carotid arteries was carried out.

The majority of operations were made under general anesthetic (205 cases). Shunting was used selectively (95 cases, 41%; placebo group, 46 cases; low-dose ASA, 49 cases) in patients with preoperative minor stroke operated on under general anesthetic (n=72), with contralateral occlusion (n=13) or with stump pressure below 25 mm Hg (n=10). Patch was used in patients with narrow internal carotid arteries or when there was a tendency of kinking (n=15). At the end of the operation, the surgeon completed the operative record including a statement if he or she considered the patient to have been given placebo or active treatment, based on operative hemorrhage. Drains were used routinely.

During and 3 days after surgery the patient received dextran 40 (Rheomacrodex; Pharmacia AB, Uppsala, Sweden) in a dose of 1000 mL the day of operation and 500 mL/d for 3 days thereafter. Heparinization was used routinely in case of shunting (5000 IU), often reversed with protamine sulfate.

After hospital discharge, the patients were followed clinically at 1, 3, 6, and 12 months, with repeated duplex scanning at 2 and 6 months.

The sample size was based on an analysis of previous data in which 12.3% of the patients developed neurological deficits within 6 months. A reduction of at least 50% was considered clinically relevant, and group size (n=225) was determined with 80% power and P<.05. The study was designed as a double-blind and placebo-controlled trial. Patients with minor stroke before surgery were separately randomized. All data on patients and end points were interpreted before the code for treatment was broken. Analyses were made according to the intention-to-treat principle. For statistical analyses χ^2 and Fisher’s tests were used. A value of P<.05 was considered significant.

The study was approved by the Ethics Committee, Lund University.

Results

Of the 232 patients included in the study, 117 received ASA and 115 placebo. The patients were well matched regarding characteristics and indications for carotid surgery (Table 1). The preoperative duplex examination revealed a median degree of stenosis in both groups of 80% (range in both groups, 20% to
95%). The contralateral carotid artery was occluded in 11 and 15 patients, respectively.

Development of perioperative or postoperative neurological end points is seen in Table 2. Stroke without complete recovery within 1 week was not seen in any ASA-treated patients within 30 days after surgery compared with 7 cases (3 periparative) in the placebo group (30-day stroke incidence, 0% and 6%, respectively; \( P=.003 \)). The two later strokes without complete recovery in the ASA group occurred in two patients who had stopped medication because of nausea and vertigo, respectively. Five of the strokes with complete recovery within 1 week were perioperative in the ASA group.

During the 6-month posttreatment period (between 6 to 12 months postoperatively) there were 3 transient ischemic attacks and one stroke from the contralateral carotid artery in the ASA group. In the placebo group, there were 1 stroke without complete recovery, 1 stroke with complete recovery, 2 transient ischemic attacks, and 1 contralateral stroke.

One patient died in the ASA group (suicide) and 5 patients in the placebo group (3 fatal myocardial infarctions and 2 fatal strokes), giving a 30-day mortality of 0.8% and 4.3%, respectively (\( P=.12 \)). At 6 and 12 months after surgery, the mortality was 3.4% and 6.0% in the ASA group compared with 8.7% and 12.2% in the placebo group, respectively, (\( P=.11 \)). The number of event-free patients not suffering from a stroke without recovery or a cerebrovascular death is shown in the Figure.

The median intraoperative bleeding was 150 mL in the ASA group (range, 0 to 1500 mL) and 100 mL in the placebo group (range, 0 to 1200 mL). The median drainage volume was 20 mL in both groups. Reoperation was performed in 9 patients in the ASA group, in 7 patients due to bleeding but starting in only one case from the arteriotomy. In 2 patients the vessels were explored because of neurological symptoms; intraoperative Doppler examination or angiography was performed but without pathological findings. The neurological deficits were normalized within 24 hours, and a further uneventful course was noted. In the placebo group, 8 patients were reoperated. Three had neurological symptoms, and their carotid arteries were explored. In two cases thrombectomy and patch closure were necessary. Two of these patients had neurological deficits remaining for more than 7 days. Five patients were reoperated because of bleeding.

All patients with a neurological event stopped their study medication, and further treatment was individualized. Another 13 patients in the ASA group discontinued the treatment (3 with gastritis or peptic ulcers, 1 nausea, 2 vertigo, 1 vasculitis, and 2 bleeding complications; 4 wished to withdraw from the study). In the placebo group, 8 patients stopped the treatment (1 with gastritis, 1 nausea, 1 vertigo, 1 rhinitis, and 1 bleeding complication; 2 wished to withdraw). The 3 patients with bleeding complications had bleeding of a diffuse type from the surgical wound at reoperation, which was the reason the treatment was stopped.

Based on intraoperative bleeding, the opinion of the surgeon as to which group each patient belonged was registered. In the ASA group, he considered that ASA had been given to 46% and placebo to 54%. In the placebo group, the surgeons were more correct (\( P<.001 \)), and ASA was considered to have been given to 22% and placebo to 78%.

### Discussion

The effect of antiplatelet therapy as an adjunct to carotid endarterectomy has not been thoroughly investigated. Despite this, extrapolation from medical series where both a risk reduction for stroke and cardiac death have been found has made antiplatelet therapy in the postoperative period common. However, antiplatelet

Graph shows number of event-free patients in the placebo group and low-dose ASA-treated group not suffering from a stroke, without recovery or cerebrovascular death.

<table>
<thead>
<tr>
<th>Table 2. Neurological Events According to Intention-to-Treat Principle Seen 1 and 6 Months After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Stroke without complete recovery</td>
</tr>
<tr>
<td>Stroke with complete recovery</td>
</tr>
<tr>
<td>All strokes</td>
</tr>
<tr>
<td>TIA or amaurosis fugax</td>
</tr>
<tr>
<td>Contralateral TIA</td>
</tr>
<tr>
<td>Contralateral stroke</td>
</tr>
<tr>
<td>All neurological events</td>
</tr>
<tr>
<td>All deaths</td>
</tr>
<tr>
<td>Cerebrovascular deaths</td>
</tr>
</tbody>
</table>

Placebo group, \( n=115 \); ASA group, \( n=117 \); TIA indicates transient ischemic attack.
therapy cannot be given without risk, for instance, for bleeding.

In previous studies from our department where no adjuvant pharmacological treatment was used—except for intraoperative and early postoperative use of dextran—a 2% to 3% risk for in-hospital postoperative neurological deficits was seen, and for the first 6-month period a high incidence of 12% was noted, whereafter a sharp decline to about 1% risk per year was found.\textsuperscript{12,13} Based on these findings, we considered it important to extend the pharmacological treatment to the first 6-month period and to analyze the effect during this time. Therefore, this placebo-controlled double-blind study evaluating low-dose ASA (75 mg) treatment was decided.

A few patients did not fulfill the criteria to participate in the study, and some patients denied participation. Otherwise, this series represents consecutive patients. The trial period extended over 5 years. During that time, new data were published about the benefit from ASA to prevent cardiac mortality, and an increased use of ASA in the population was noted.\textsuperscript{6-8} Although the patients in the study were instructed not to use nonsteroidal anti-inflammatory drugs during the study period, it seems probable that a few patients used such treatment despite the instructions given. It also seems probable that a few patients prescribed active treatment did not regularly comply to take the treatment daily, even if they stated to have done so at the follow-up. This lack of compliance has been recently shown in patients after femoropopliteal bypass reconstructions.\textsuperscript{14} Nevertheless, this fact should reduce the possibility to show any benefit from ASA. During the treatment, no objective laboratory tests were used to control serum ASA levels and thereby compliance to given instructions. Conversely, such a control only gives information for a limited period of the 6 months of prophylaxis.

The groups did not differ in risk factors and demographic data. There is a tendency (P=0.12) that all neurological events during the 6-month study period were reduced in the ASA group. If one only considers stroke without complete recovery within 1 week, the difference was significant. In the ASA group, there were only 2 persistent strokes (both patients had stopped active treatment before having the stroke) compared with 11 strokes without complete recovery in the placebo group (P=0.01). Additionally, the number of contralateral strokes and mortality also speaks in favor of ASA treatment. Our rate of stroke within 6 months and without complete recovery was 1.7% in the ASA-treated group, a rate that is in accordance with the results from the European and North American multicenter trials.\textsuperscript{8,10}

Intraoperative bleeding and the number of reoperations for bleeding did not differ nor could the surgeon predict whether ASA treatment had been given. The number of patients who discontinued the treatment was comparable.

There has been much debate on the dose of ASA. However, studies have shown that the effect on the prostanoïd system is effective also with the low dose used in this study.\textsuperscript{14} Recently, two clinical studies have used low-dose ASA (30, 160, 283 mg) with good effect and less complications from the low-dose therapy.\textsuperscript{15,16} Comparative studies evaluating low-dose and high-dose therapy are lacking.

In conclusion, ASA (75 mg/d) appears to reduce the risk for stroke without complete recovery within 6 months after carotid endarterectomy, and there is a tendency also for lowering all neurological events and mortality by such treatment. The number of negative effects was few and minor. The use of 75 mg/d ASA appears to be safe but still effective. Further studies confirming our data would be of value before firm recommendations can be given. However, with other series on the beneficial effect of ASA it seems reasonable to offer endarterectomized patients ASA for cerebrovascular protection perioperatively and postoperatively, at least for 6 months.

Acknowledgment

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References

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